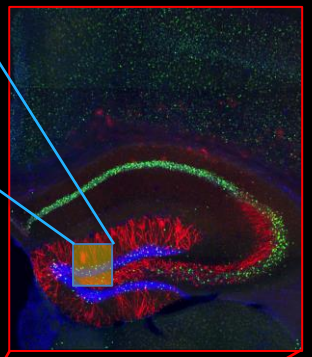
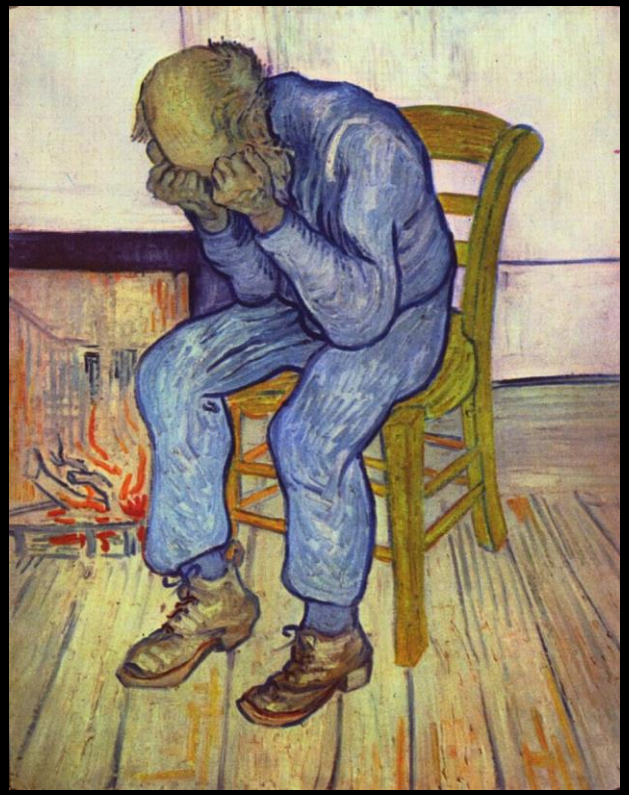
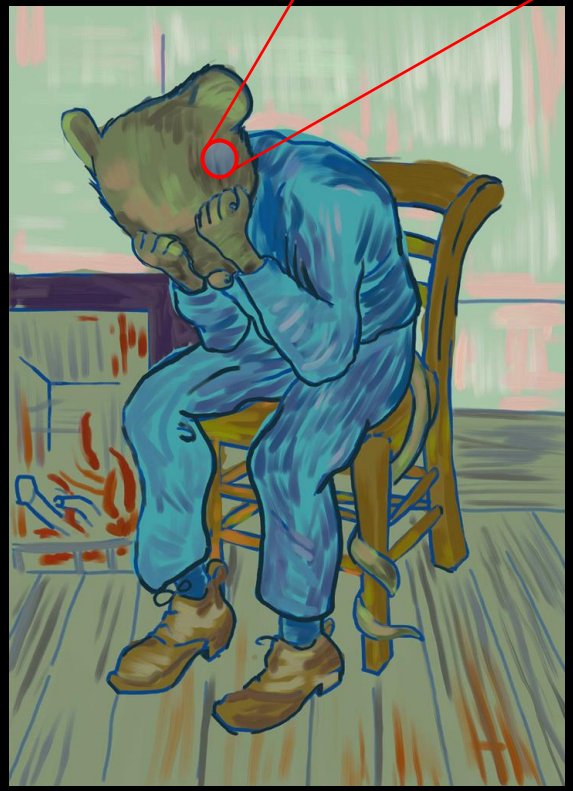
Activating positive memory engrams suppresses depression-like behavior







Steve Ramirez
MIT

Today's Forecast

1) Beginning
- The kinds of memories worth manipulating

2) Middle
- Acutely rescuing psychiatric disease-related states

3) End
- Chronically manipulating memories to achieve long-lasting antidepressant-like effects

COMMENTARY

PSYCHIATRIC DRUG DISCOVERY

Revolution Stalled

Steven E. Hyman

Drug discovery is at a near standstill for treating psychiatric disorders such as schizophrenia, bipolar disorder, depression, and common forms of autism. Despite high prevalence and unmet medical need, major pharmaceutical companies are deemphasizing or exiting psychiatry, thus removing significant capacity from efforts to discover new medicines. In this Commentary, I develop a view of what has gone wrong scientifically and ask what can be done to address this parlous situation.

Neuron
Perspective

Twenty-Five Years of Progress: The View from NIMH and NINDS

Thomas R. Insel[1,*] and Story C. Landis[2]
[1]National Institute of Mental Health, 6001 Executive Boulevard, Room 8129, MSC 9669, Bethesda, MD 20892-9669, USA
[2]National Institute of Neurological Disorders and Stroke, 31 Center Drive, Building 31, Room 8A52, MSC 2540, Bethesda MD 20892-2540, USA
*Correspondence: tinsel@mail.nih.gov
http://dx.doi.org/10.1016/j.neuron.2013.09.041

What can we do?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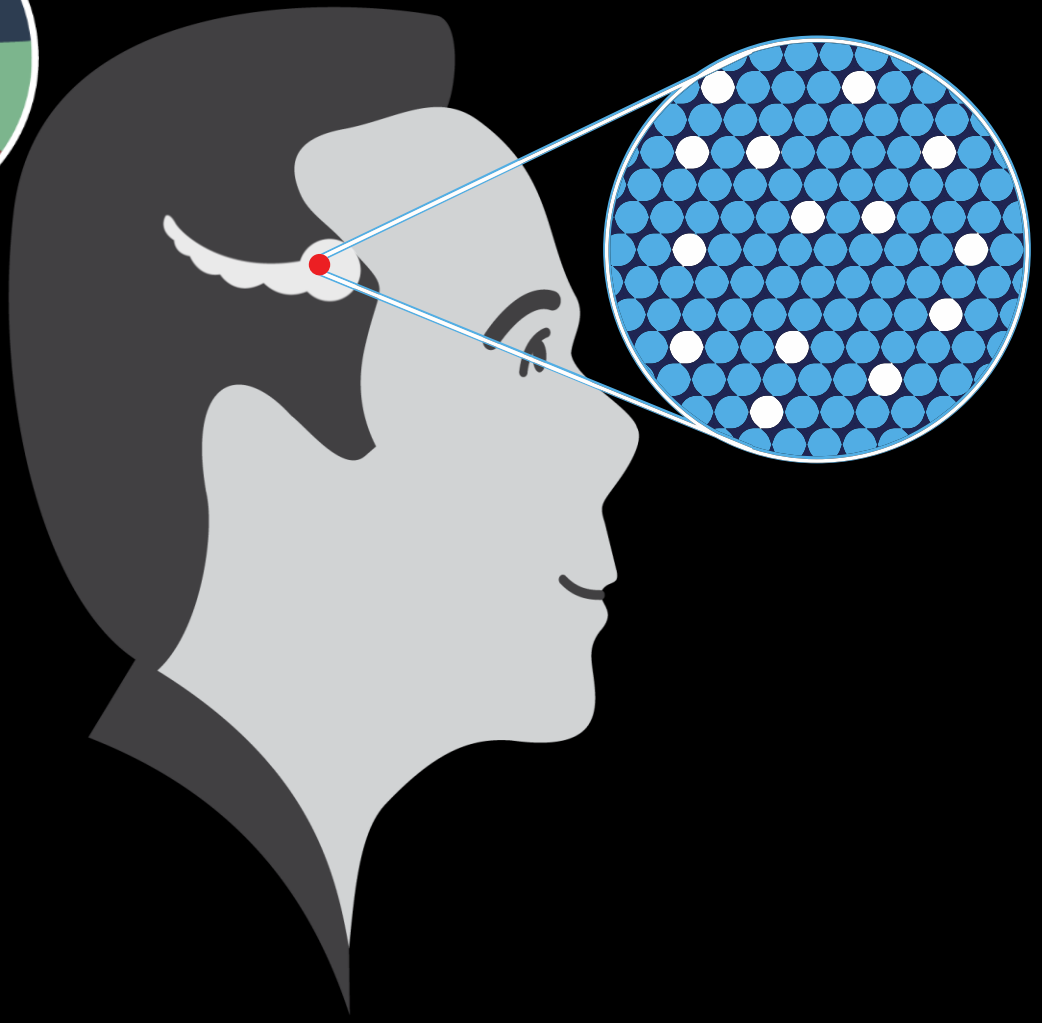
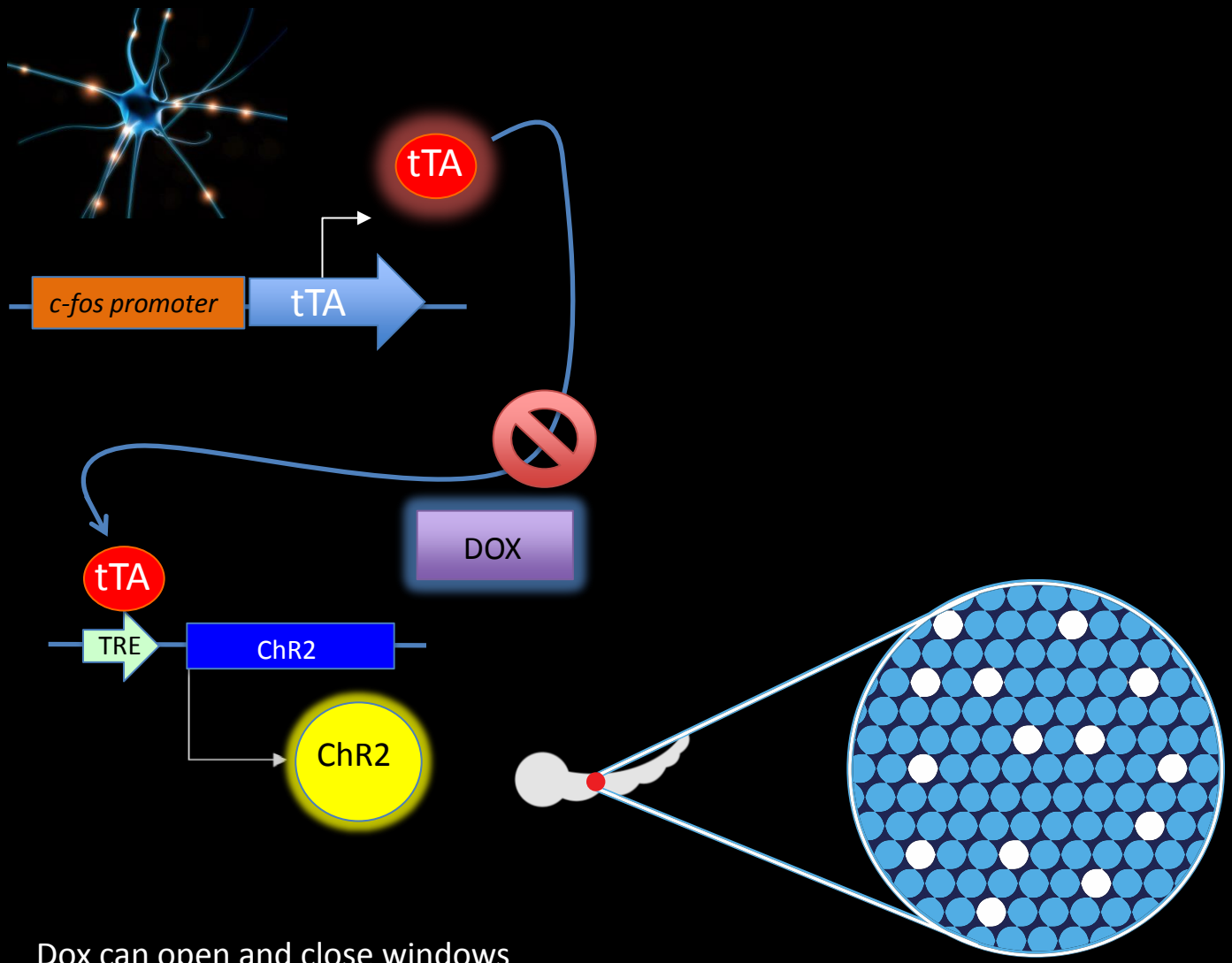
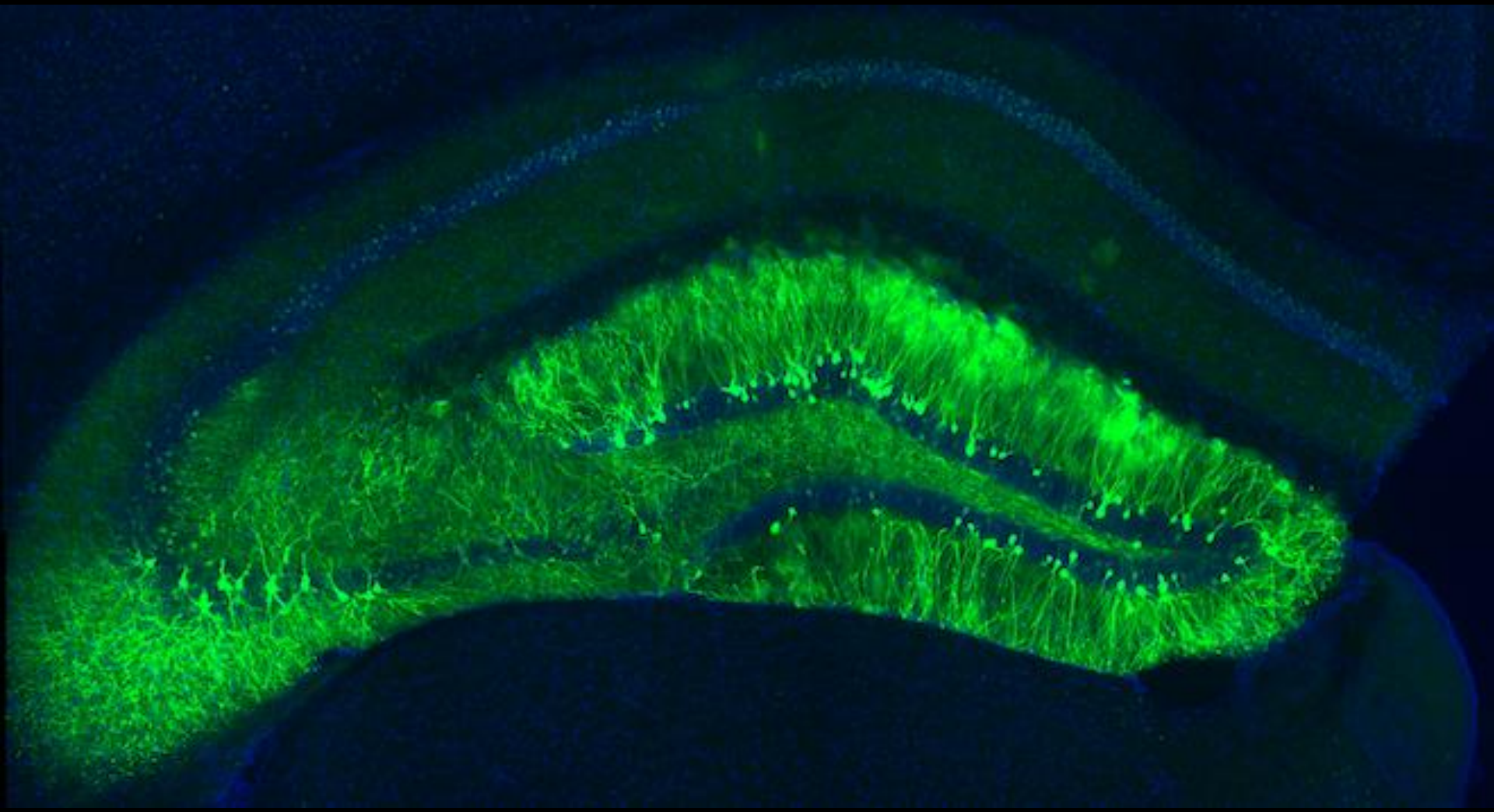


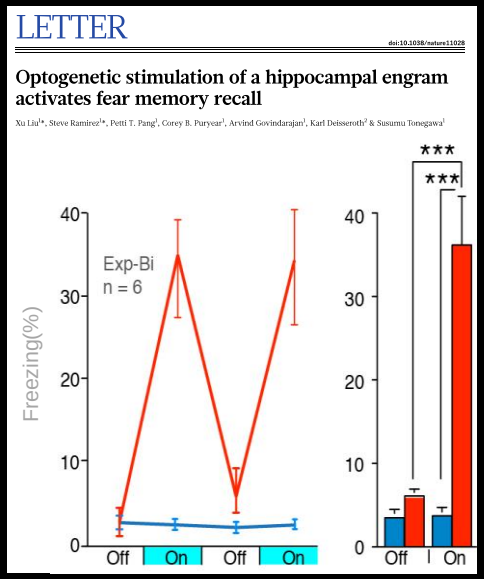


Dox can open and close windows for expressing a given gene in an activity-dependent manner

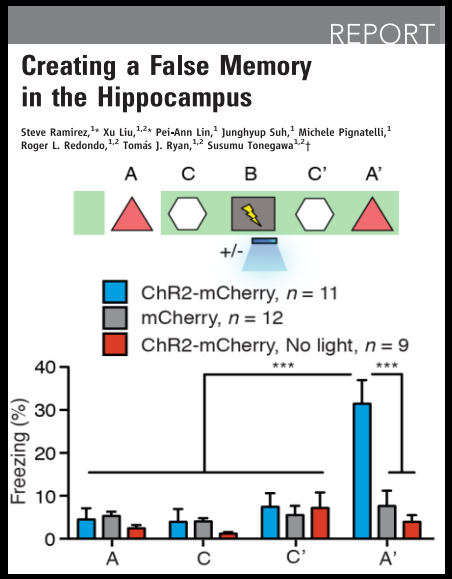


Where we are; where we're going

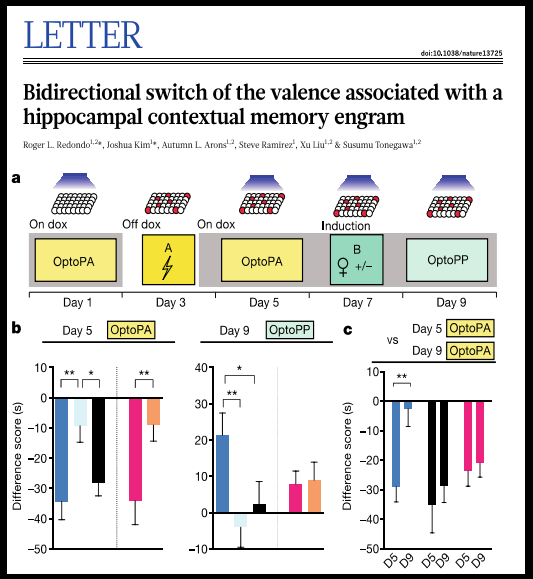
1) Proof of concept:
Activating fear expression



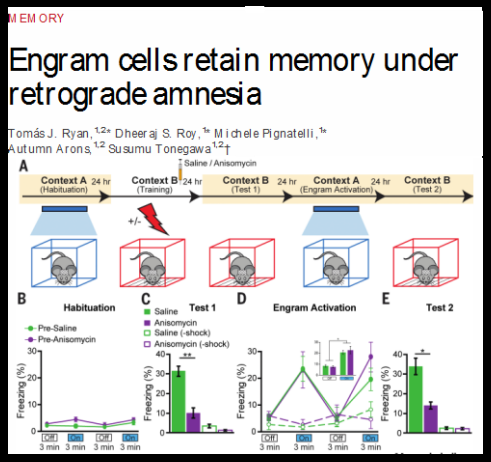
2) Application:
Artificially creating CS-US assoc.



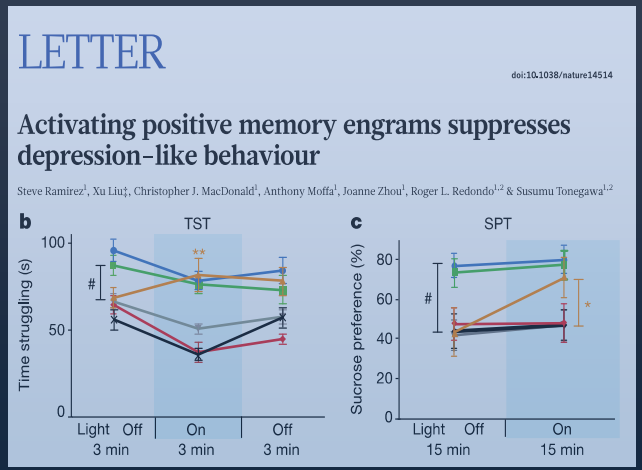
3) Revealing new theory:
Driving fear and reward



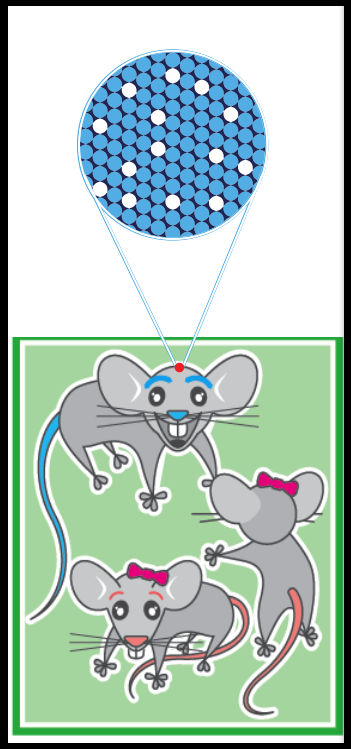
4) Identifying plasticity in DG cells
(Ryan et al. *Science*, 2015)

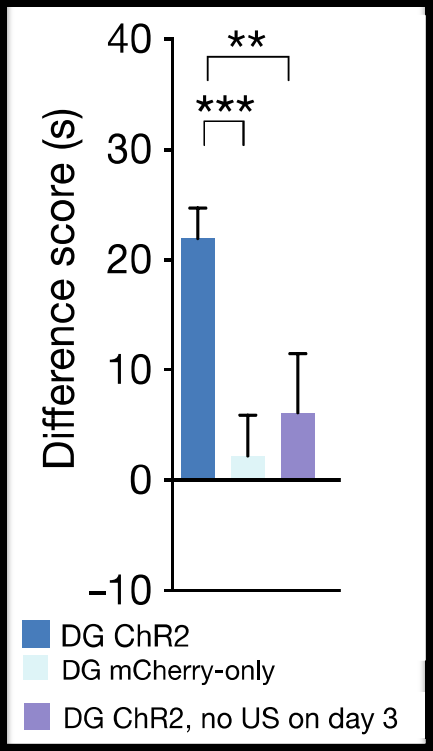


5) Using memory to fix impaired cognition
(Ramirez et al. *Nature*, 2015)

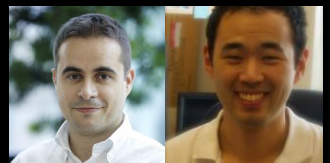


Activating DG cells associated with a positive experience





Significance: DG cells that were active during reward conditioning can drive place preference.



(Redondo and Kim et al., *Nature,* 2014)

Hypothesis

Hippocampus cells active during the encoding of a positive experience are sufficient to rescue stress-induced maladaptive behavior when reactivated.

- These behaviors include responses to challenging situations where active vs. passive action patterns can be measured
  (i.e. the tail suspension test)
- The inability to experience or seek out pleasure, or anehdonia
  (i.e. the sucrose preference test.)
- And a variety of assays measuring anxiety-like behaviors
  (i.e. open field and elevated plus maze)

Today's Forecast

1) Beginning
- The kinds of memories worth manipulating

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- Acutely rescuing psychiatric disease-related states

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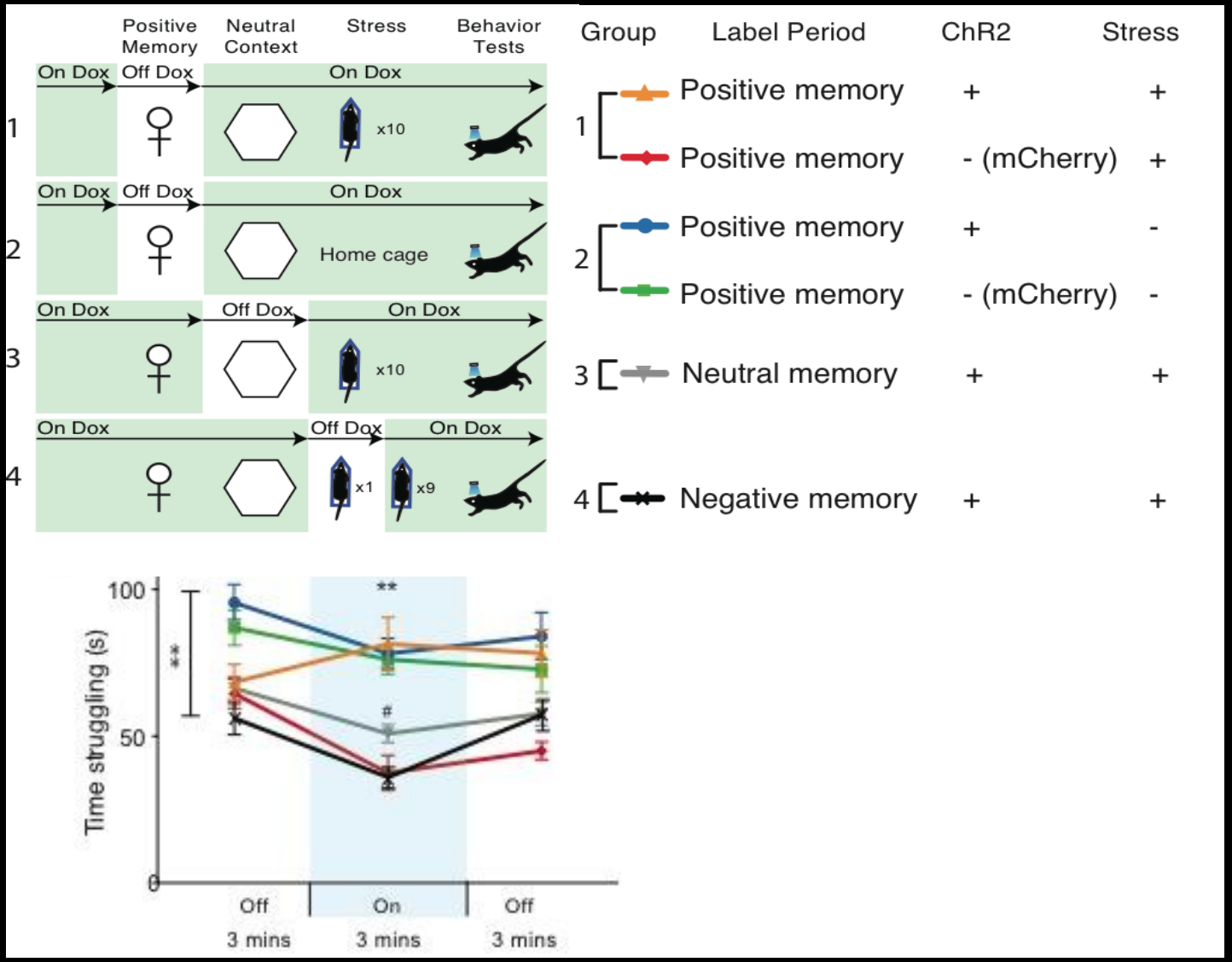
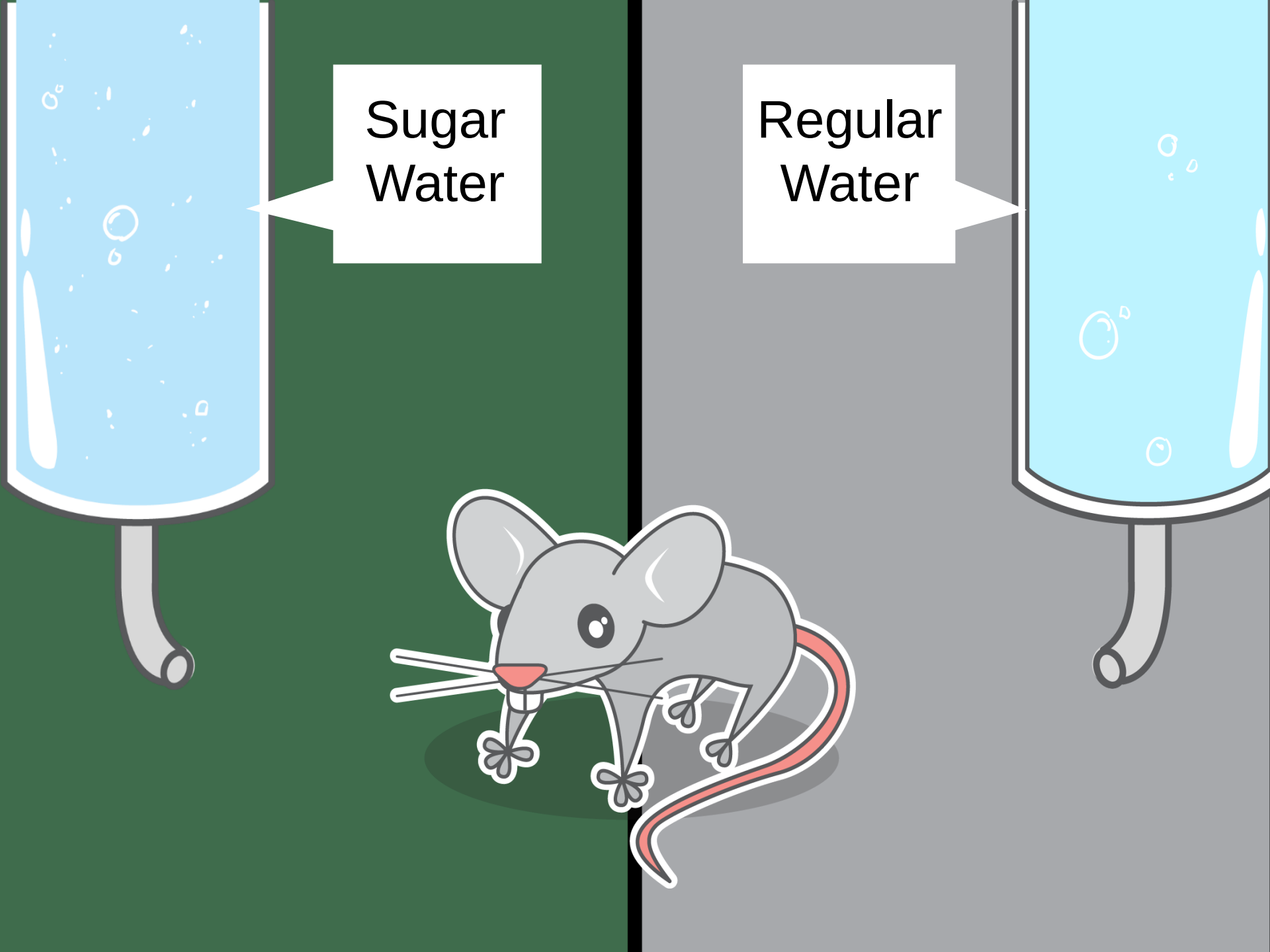
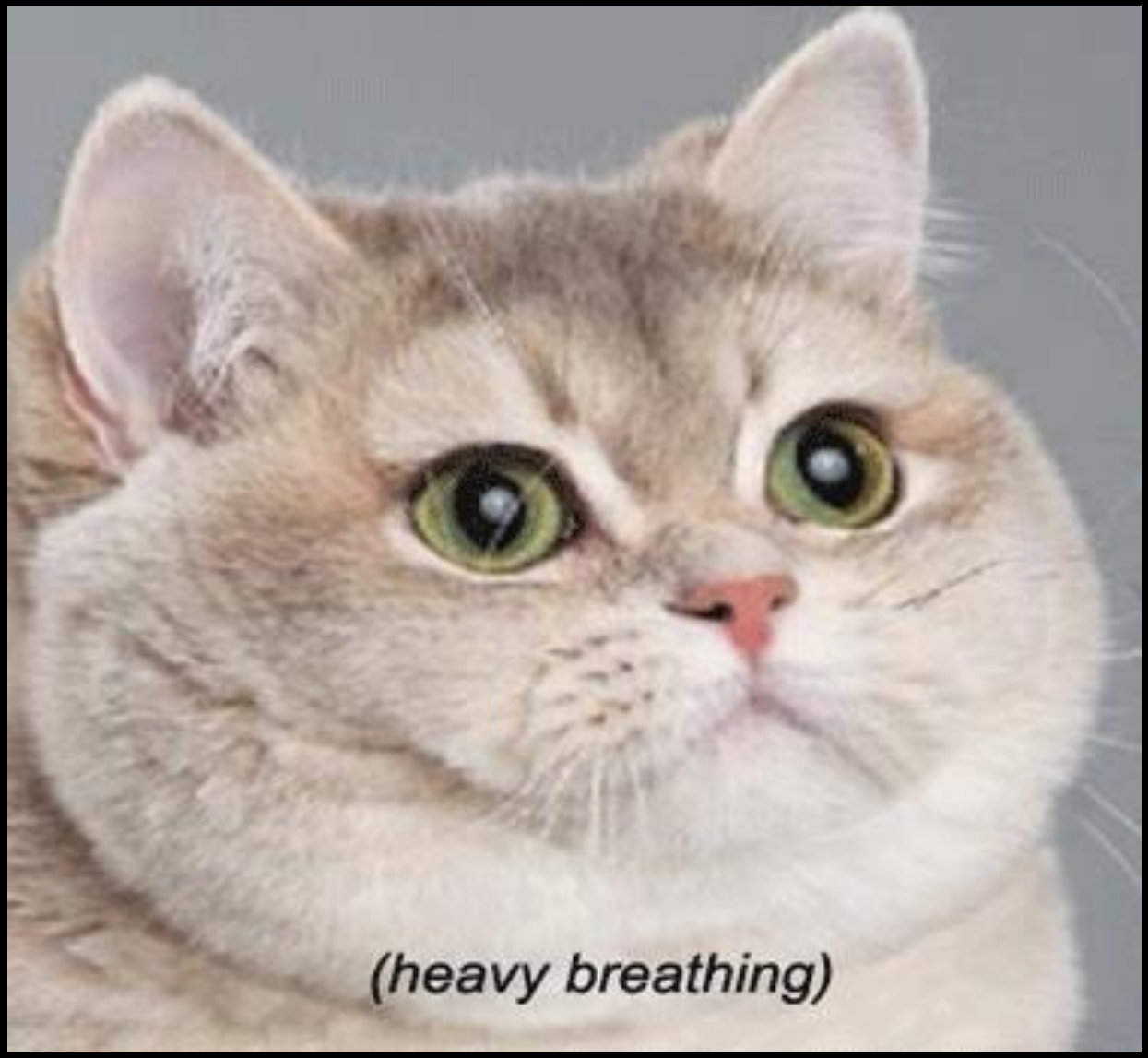
- Chronically manipulating memories to achieve long-lasting antidepressant-like effects

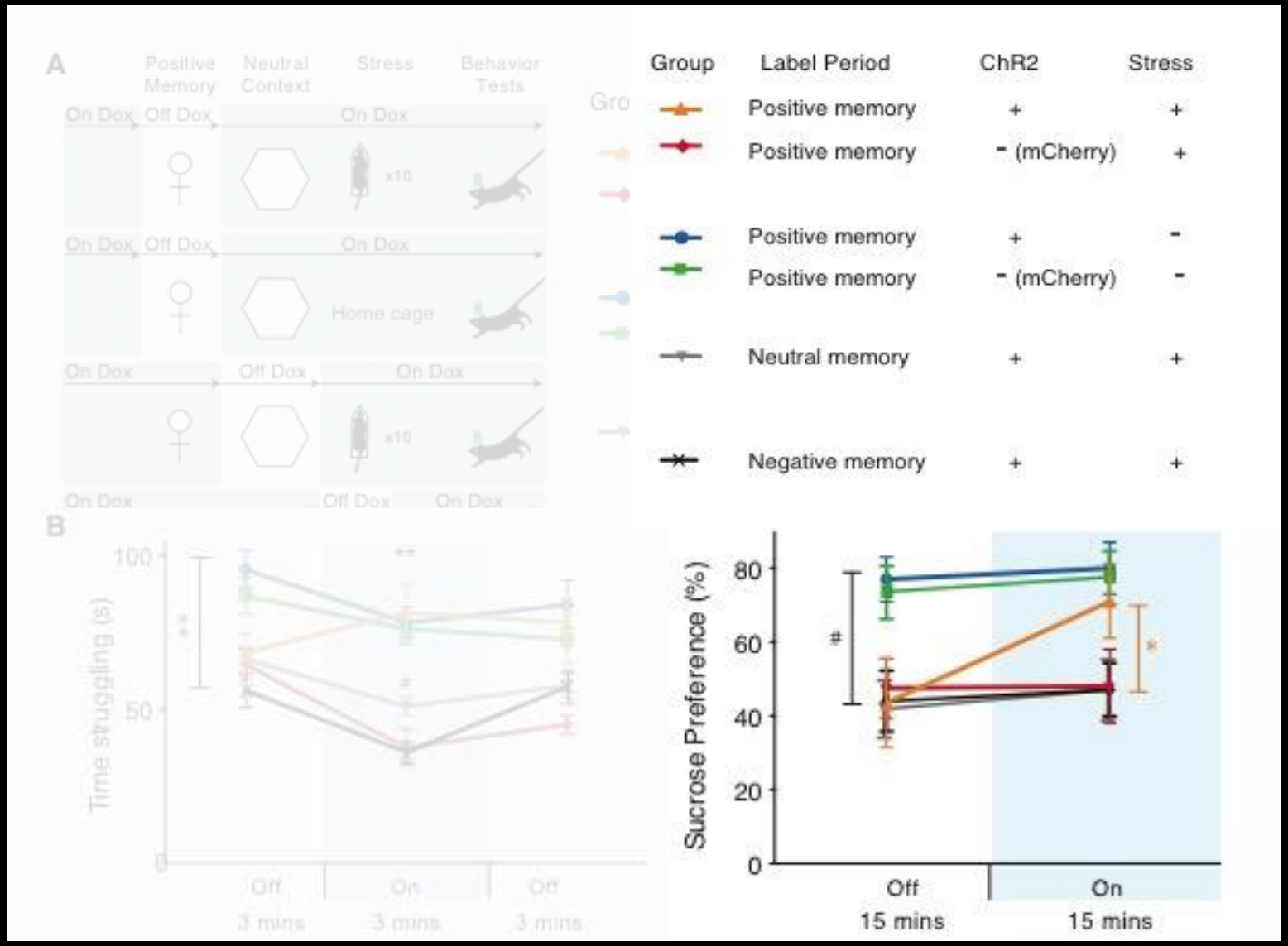
Activated positive memories are sufficient to reverse stress-induced behavioral impairments



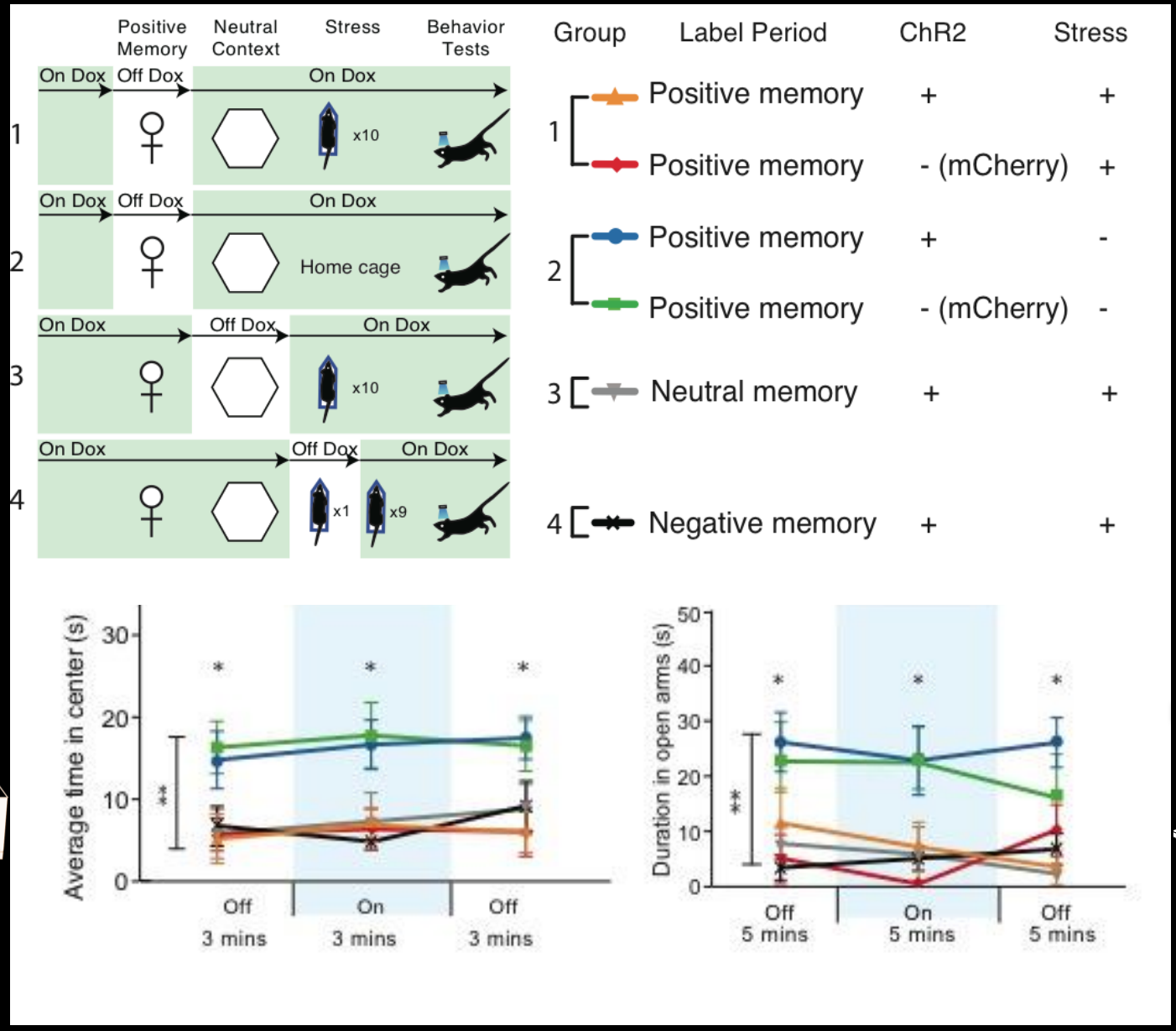

Sugar Water
Regular Water

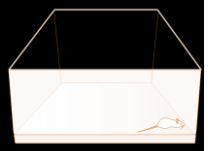

(heavy breathing)

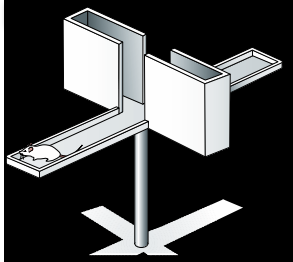
DG cells associated with a positive experience are sufficient to reverse stress-induced behavioral changes



Activated positive memories do not alter anxiety-like behavior

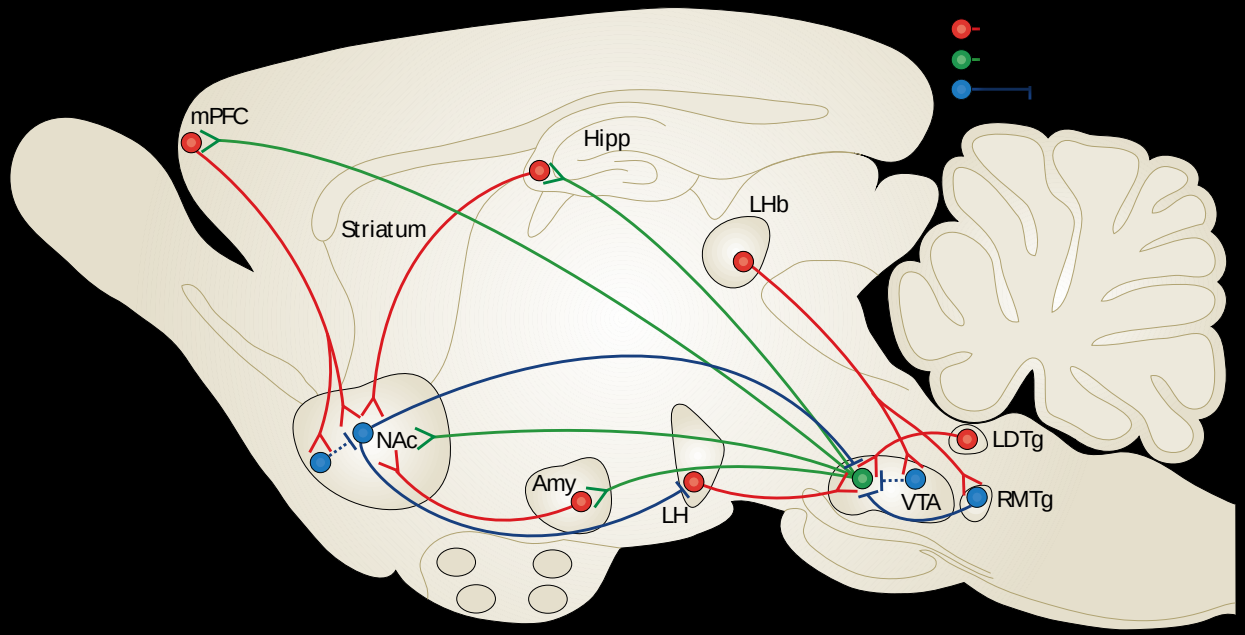






(Cryan and Holmes, 2005)

What is the interaction between active positive memories and a brain in a stress-induced state?



The brain reward circuitry in mood disorders

Scott J. Russo and Eric J. Nestler

Abstract | Mood disorders are common and debilitating conditions characterized in part by profound deficits in reward-related behavioural domains. A recent literature has identified important structural and functional alterations within the brain's reward circuitry — particularly in the ventral tegmental area–nucleus accumbens pathway — that are associated with symptoms such as anhedonia and aberrant reward-associated perception and memory. This Review synthesizes recent data from human and rodent studies from which emerges a circuit-level framework for understanding reward deficits in depression. We also discuss some of the molecular and cellular underpinnings of this framework, ranging from adaptations in glutamatergic synapses and neurotrophic factors to transcriptional and epigenetic mechanisms.

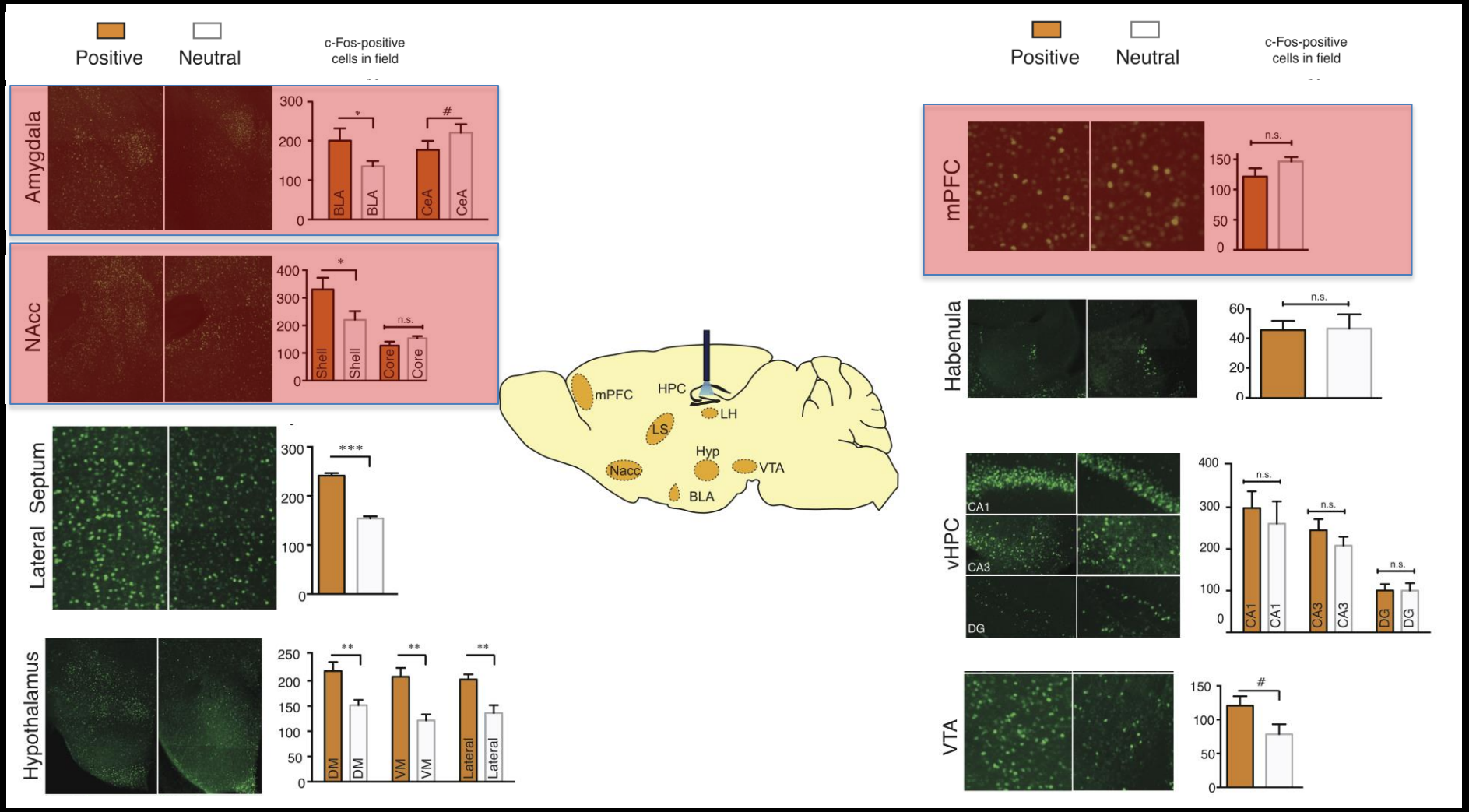
Table 1 | Comparison of brain imaging and post-mortem studies in human depression

Brain region	Human imaging results	Human post-mortem analysis
Nucleus accumbens	↓ Volume ↓ BOLD signal during reward-related task	↓ Expression of synaptic remodelling gene *RAC1*
Ventral tegmental area	NA	NA
Hippocampus	↓ Volume ↓ BOLD signal during positive word-encoding task	↓ Synapse density ↓ Glial cell density
Basolateral amygdala	↓ Volume ↑ Resting-state BOLD signal	↓ Grey matter ↓ Glial cell density
Medial prefrontal cortex	↓ Volume ↓ BOLD signal during reversal-learning task	↓ White matter ↓ Dendritic branching ↓ Glial cell density

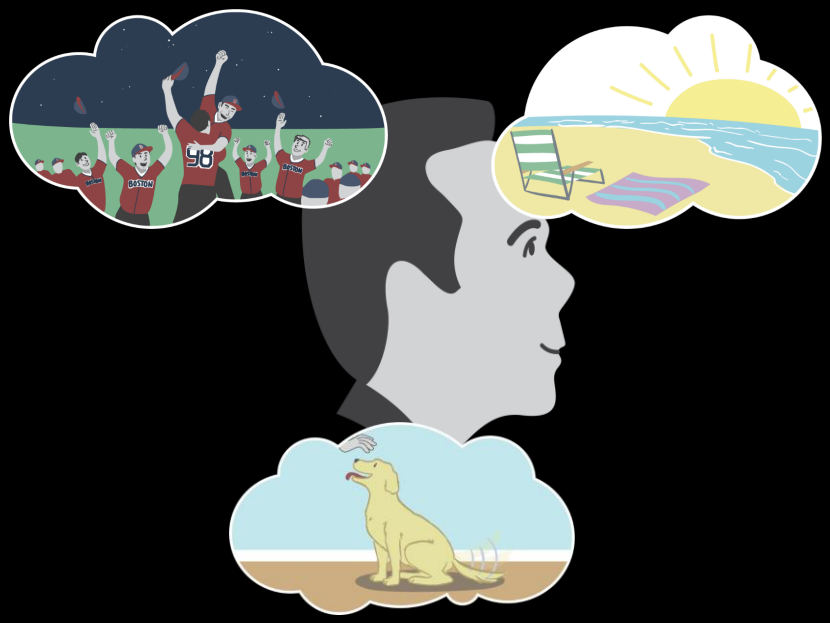
What is the interaction between active positive memories and a brain in a stress-induced state?

Significantly upregulated cFos

Did not significantly upregulate cFos



(Ramirez et al. Nature, *in press*)

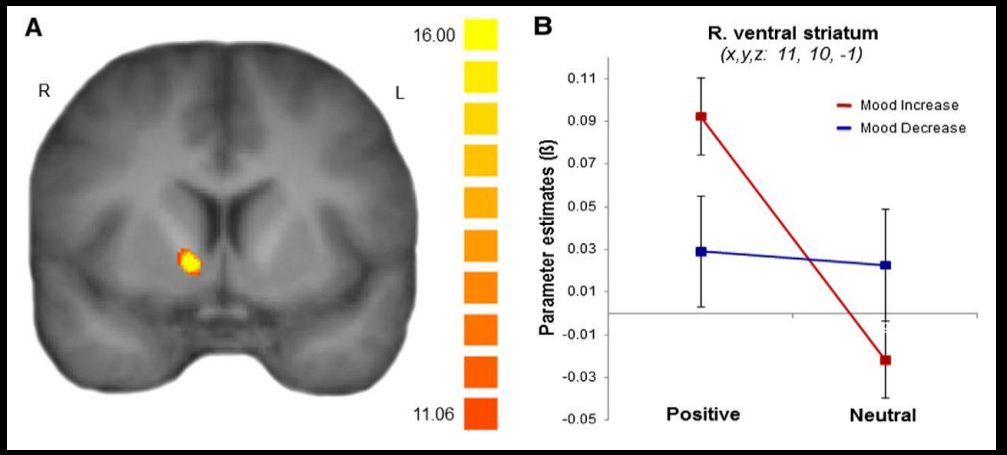


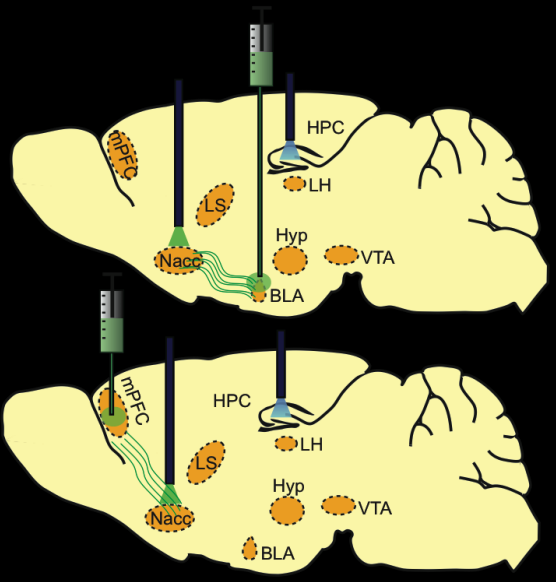
Neuron

Article

Savoring the Past: Positive Memories Evoke Value Representations in the Striatum

Megan E. Speer,[1] Jamil P. Bhanji,[1] and Mauricio R. Delgado[1,*]
[1]Department of Psychology, Rutgers University, Newark, NJ 07102, USA
*Correspondence: delgado@psychology.rutgers.edu
http://dx.doi.org/10.1016/j.neuron.2014.09.028




mPFC
HPC
LH
LS
Hyp
VTA
Nacc
BLA
mPFC
HPC
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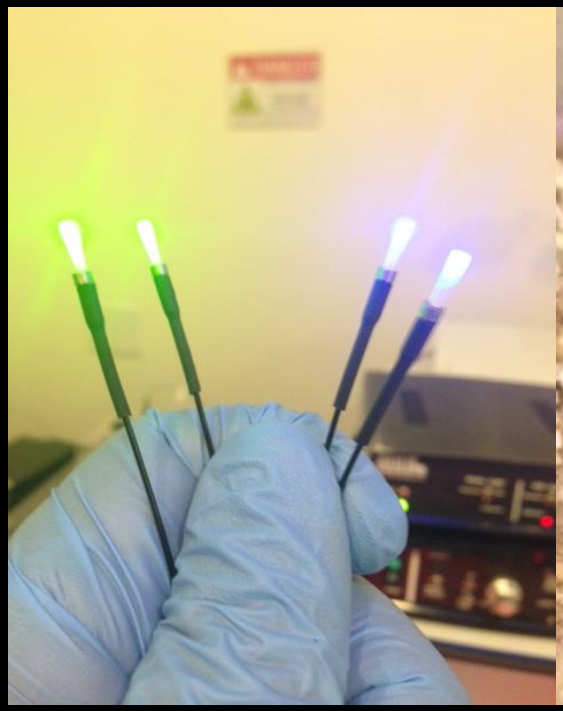
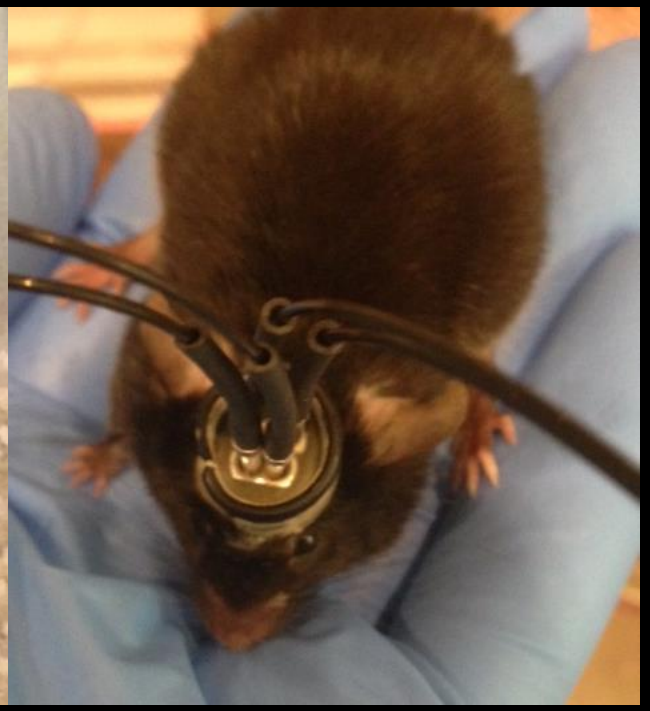
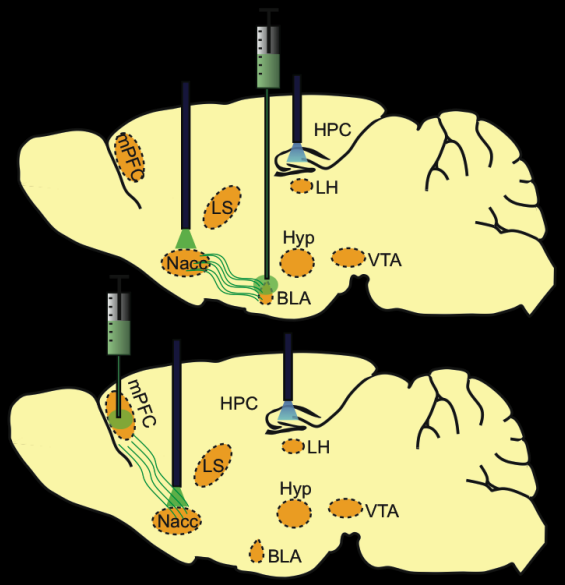
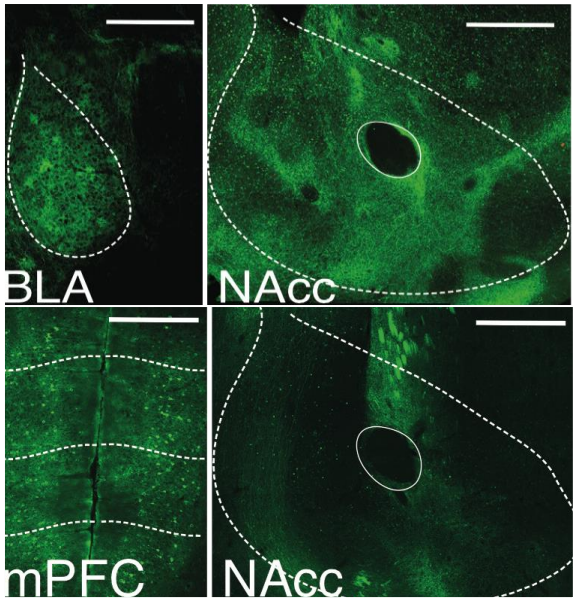
VTA
Nacc
BLA

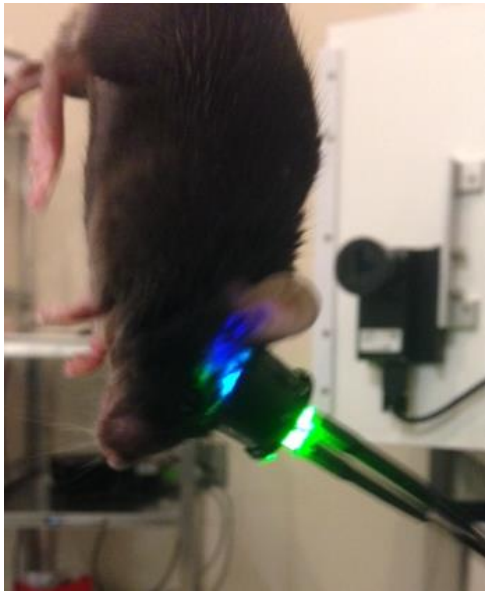


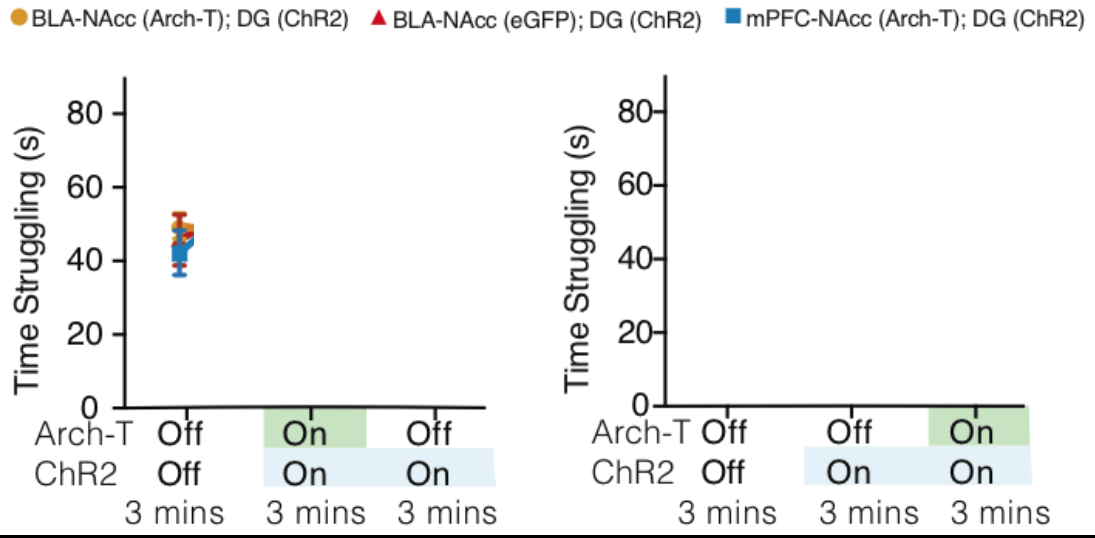


The DG-mediated acute rescue is blocked by inhibiting BLA (but no mPFC) input to NAcc

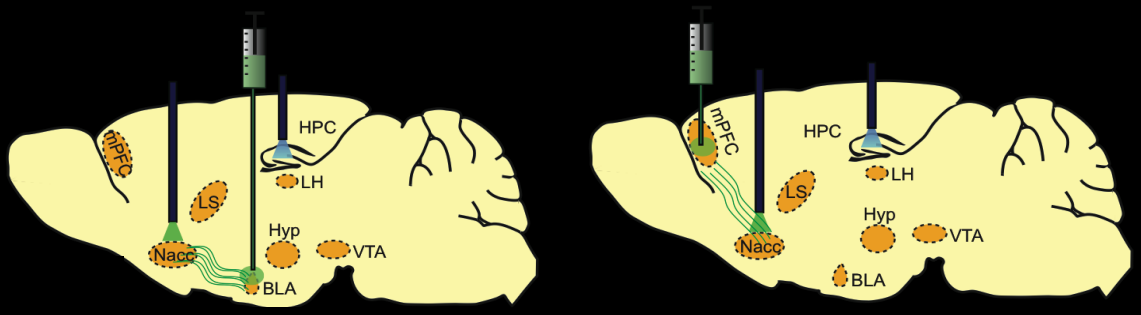


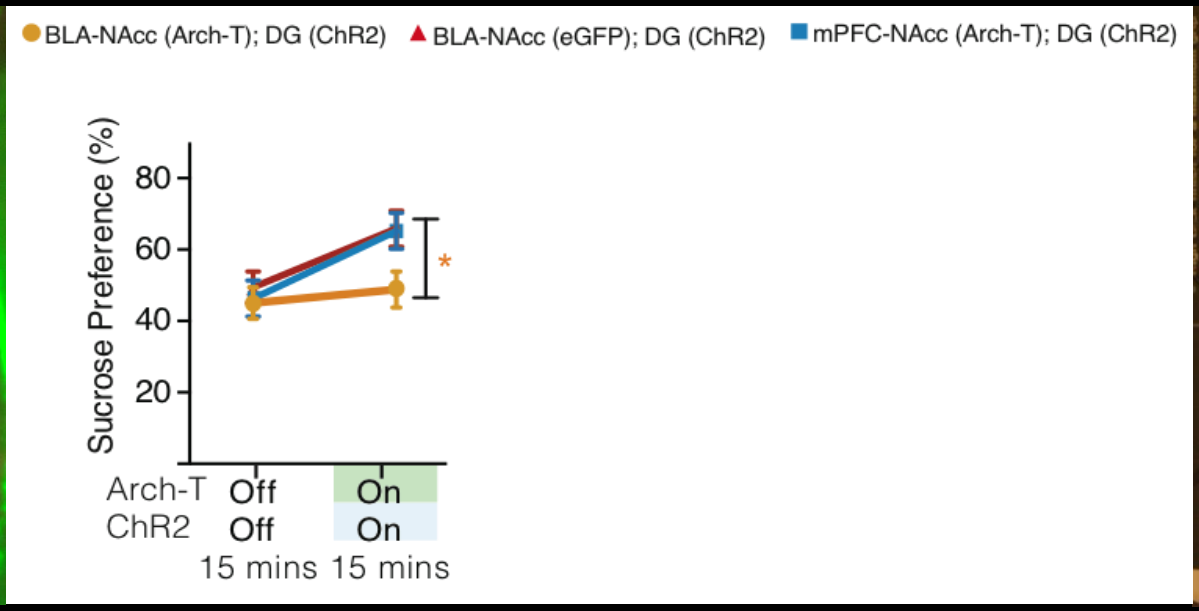






BLA to NAcc terminals are necessary for the antidepressant-like effects of DG stimulation





Significance: Inhibiting BLA:NAc terminals can "clamp down" on behavior when a DG-mediated positive memory is reactivated

Today's Forecast

1) Beginning
- The kinds of memories worth manipulating

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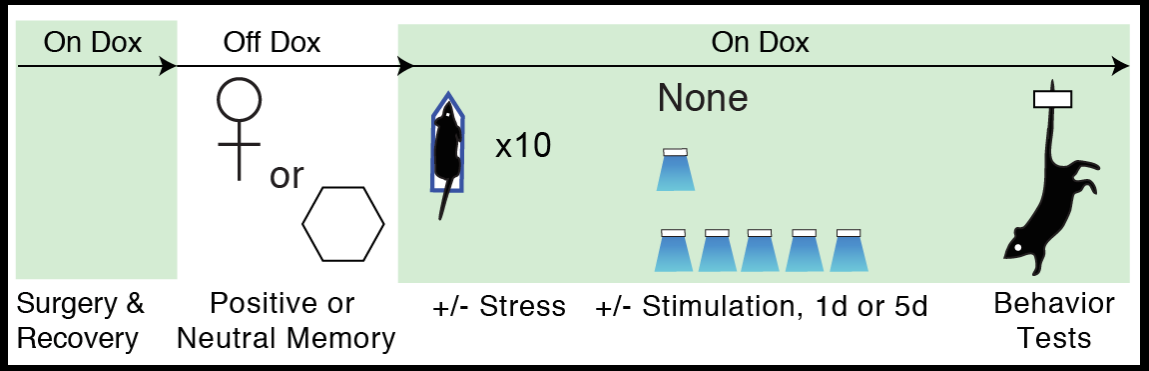
- Acutely rescuing psychiatric disease-related states

3) End
- Chronically manipulating memories to achieve long-lasting antidepressant-like effects

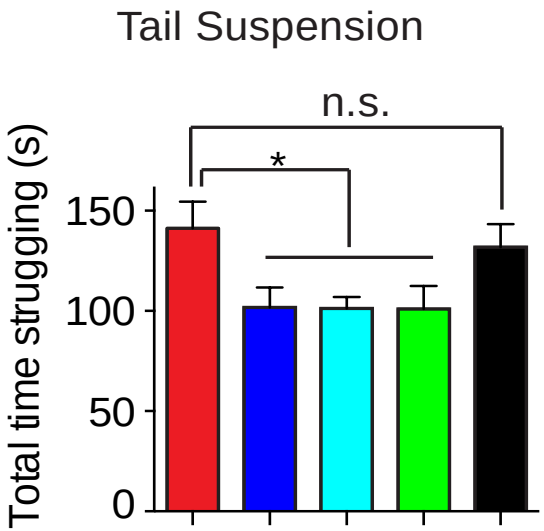
Experimental Design for Multiple Stimulations

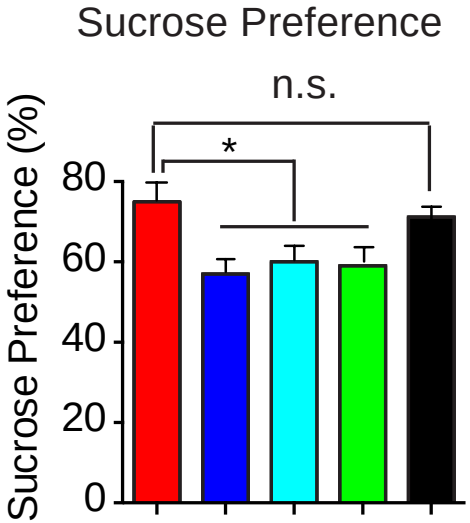


Group	Memory Labeled	Stress	Stimulation
5-day	Positive	Yes	5 days
1-day	Positive	Yes	1 day
NoStim	Positive	Yes	None
Neutral	Neutral	Yes	5 days
NoStress	Positive	No	5 days

Behavioral Improvements in the TST and SPT

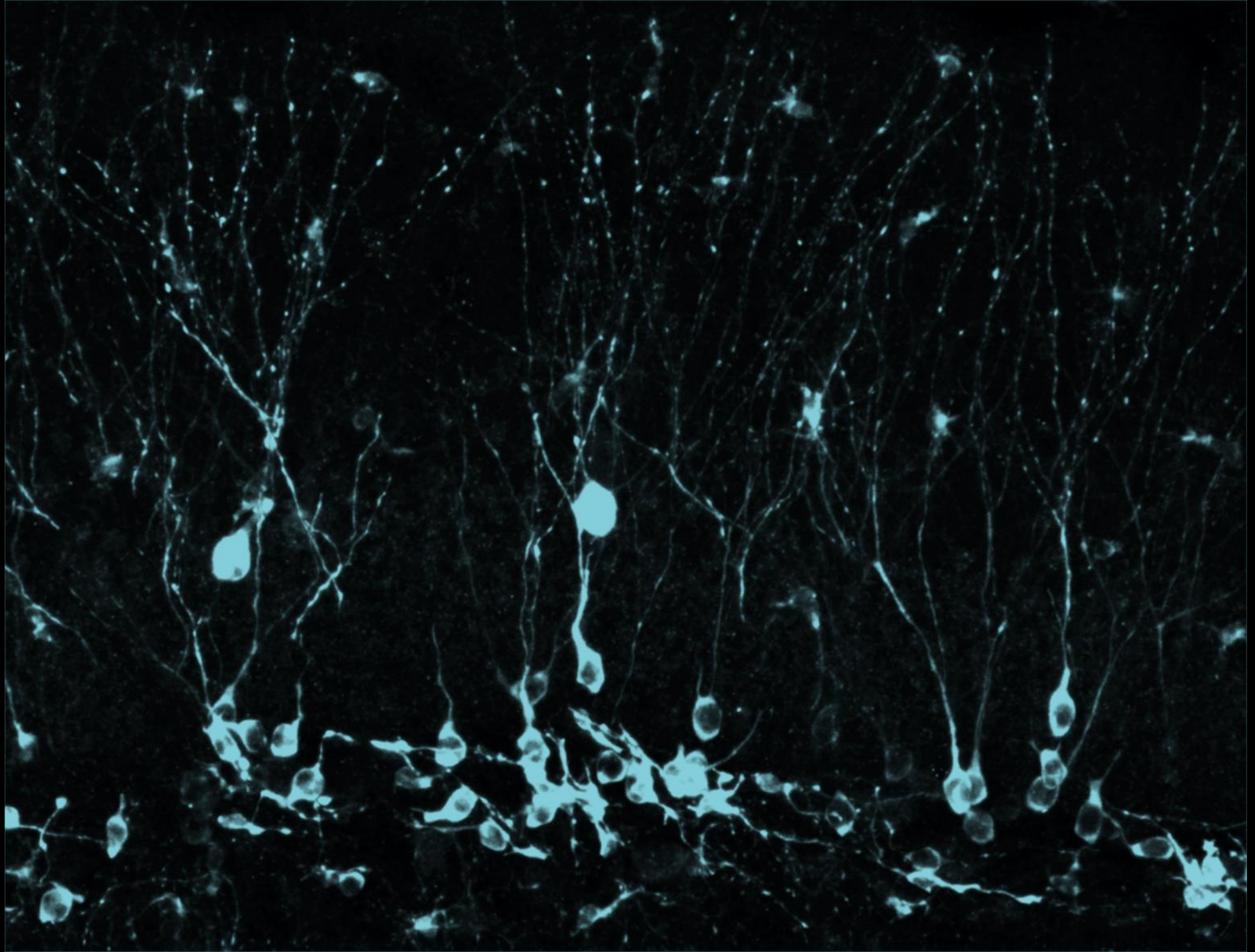
Group	Memory Labeled	Stress	Stimulation
5-day	Positive	Yes	5 days
1-day	Positive	Yes	1 day
NoStim	Positive	Yes	None
Neutral	Neutral	Yes	5 days
NoStress	Positive	No	5 days

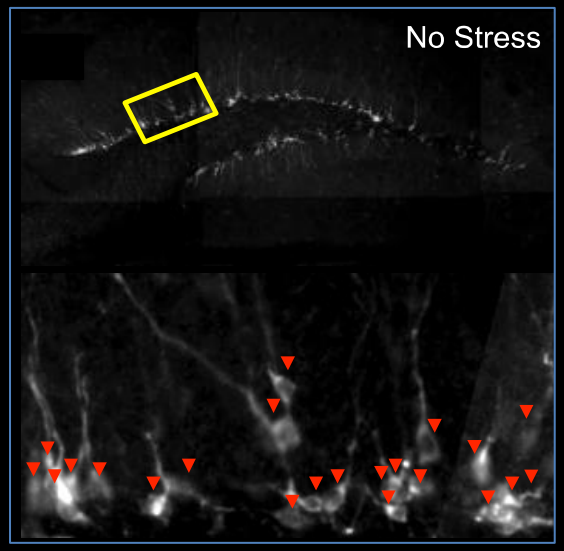


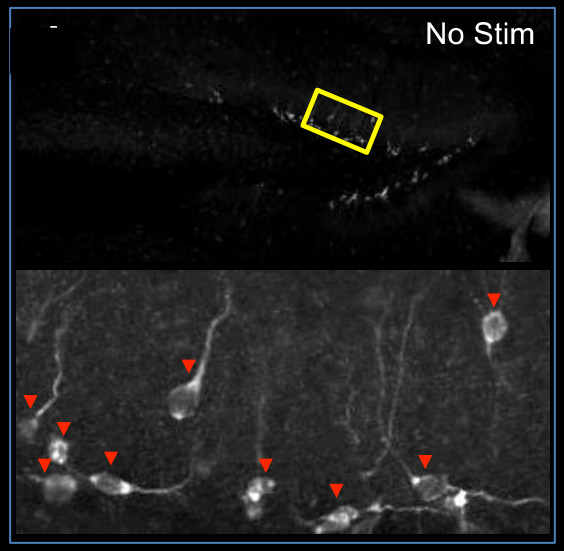


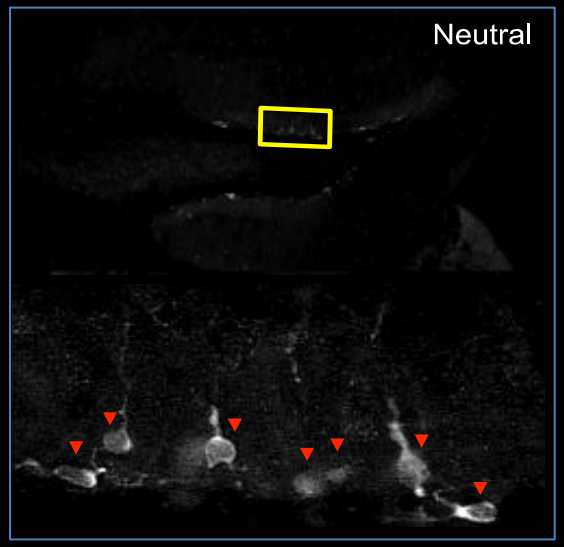
Significance: multiple reactivations of DG cells previously active during a positive experience reversed the stress-induced decreases of time struggling or preference for sucrose

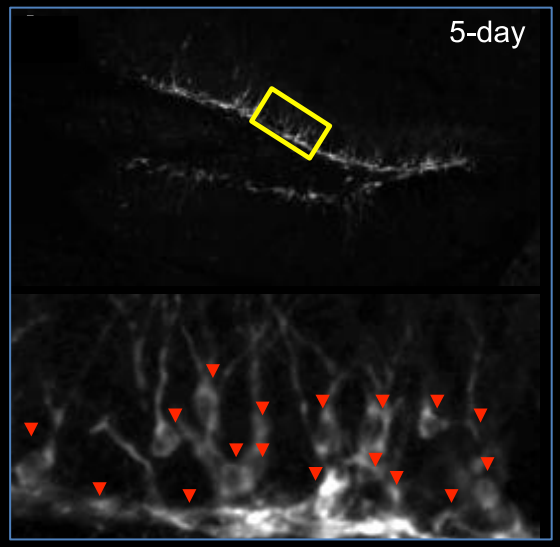
?

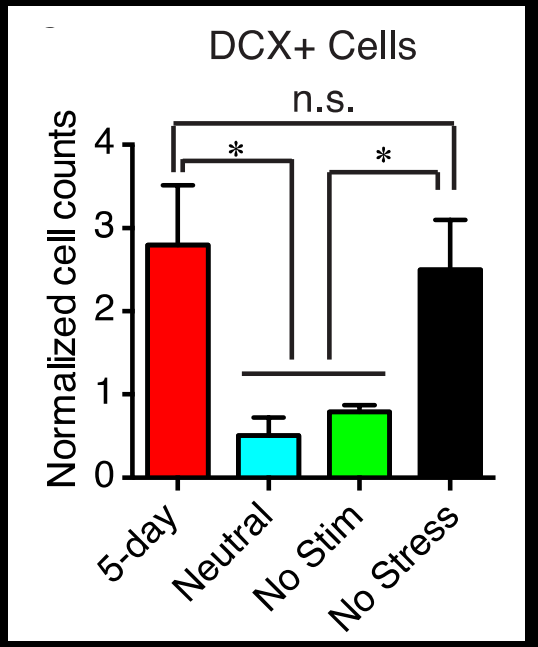












Significance: multiple activations of a positive memory reversed the decrease of neurogenesis (as measured by DCX or PSA-NCAM) caused by chronic stress

Summary and Future Directions

- Acutely activating DG cells previously active during a positive experience are sufficient to reverse the effects of stress in the TST and SPT
- These effects require real-time BLA:NAcc activity
- Chronically activating DG cells produces a long-lasting rescue of these behaviors and correlates with a rescue in neurogenesis.

- Chronic reactivation of positive or negative memories before stress to induce resilience or susceptibility?
- dHPC vs vHPC engram regulation in anxiety-related behaviors?
- Ablate neurogenesis to test if chronic positive memory activation still works?
- Pull down engram-bearing cells across brain regions and determine their transcriptional landscape?

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Roger Redondo
Tomas Ryan
Josh Kim
Dheeraj Roy
Mike Ragion
Susumu Tonegawa
The T-Lab

LETTER

doi:10.1038/nature14514

Activating positive memory engrams suppresses depression-like behaviour

Steve Ramirez[1], Xu Liu‡, Christopher J. MacDonald[1], Anthony Moffa[1], Joanne Zhou[1], Roger L. Redondo[1,2] & Susumu Tonegawa[1,2]